

## REMARKS

Claims 52, 56, 58-61, 63, 66 and 68-73 were pending prior to this Response. Applicants cancel Claim 52 and amend Claims 56, 58-61, 63, 66, 72 and 73. Claims 56, 58-61, 63, 66 and 68-73 will be pending after this Response. Applicants thank the Examiner for the time spent on the consideration of the claims and applicants' previous response.

### Support for the Amendments

The amendments and the new claims do not add any new matter and are supported throughout the application, as filed. Claims 56, 58, 59, 60, 61, 66 and 73 are amended to change their dependency. Support for the amendments to Claim 63 is found, for example, on page 14, lines 19-23, of the specification. Support for the amendment to Claim 72 is found, for example, on page 15, line 25, of the specification.

### Rejections under 35 U.S.C. §103(a)

MPEP 2142 states: "To reach a proper determination under 35 U.S.C. §103, the examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made. In view of all the factual information, the examiner must then make a determination whether the claimed invention 'as a whole' would have been obvious at that time to that person." To reject a claim as obvious, the Examiner, first, must resolve the *Graham* factual inquiries, namely, (a) determining the scope and content of the prior art, (b) ascertaining the differences between the claimed invention and the prior art, and (c) resolving the level of ordinary skill in the pertinent art. *See* MPEP 2141(II) citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

***Eyles (Vaccine Vol. 16(7):698-707 (1998); "Eyles") and Amsden et al. (WO 99/57176; "Amsden")***

The Examiner rejects Claims 52, 56, 58-61, 66 and 68-73 under 35 U.S.C. §103(a) as obvious over *Eyles* in view of *Amsden*. Applicants cancel Claims 52, thereby rendering its rejection moot. Applicants request the Examiner to withdraw the rejection of Claims 56, 58-61, 66 and 68-73 at least due to the reasons discussed below.

Dependent Claims 66 and 68-71 are Nonobvious in View of Eyles and Amsden at Least for the Same Reasons Claim 63 is Nonobvious

The Examiner does not reject Claim 63 in this section. Applicants therefore conclude that the Examiner finds that the combination of elements recited in Claim 63 would have been nonobvious to one of ordinary skill in the art in the area of the present application, at its priority date. Applicants amend Claim 66 to depend on Claim 63. Applicants submit to the Examiner's attention that Claim 66 (as currently amended) and Claims 68-71 (as previously presented) are dependent, directly or indirectly, on Claim 63. Accordingly, Claims 66 and 68-71 recite at least the same combination of elements as Claim 63 and should be found nonobvious in view of Eyles and Amsden for at least the same reasons Claim 63 is nonobvious. Applicants request the Examiner to issue appropriate statements and withdraw the rejection of Claims 66 and 68-71.

Nonobviousness of Claim 72 and Its Dependent Claims 56, 58-61 and 73

*The Office Action fails to Provide a Clear Articulation of Reasons why the Claims Would Have Been Obvious*

Applicants assert that the combination of Eyles and Amsden fails to render obvious Claim 72 and its dependent Claims 56, 58-61 and 73. Applicants discussed the scope and content of Eyles and Amsden at least in the Amendment and Response to Final Office Action filed February 13, 2009, in the Amendment and Response to Non-Final Office Action filed August 31, 2009, and in the Amendment and Response to Final Office Action filed March 8, 2010 ("previous responses"). Applicants maintain the positions stated in the previous responses and respectfully request the Examiner to refer to their previously submitted remarks characterizing the cited documents.

Applicants understand the Examiner's analysis supporting the rejection in view of Eyles and Amsden as follows. Eyles describes immunogenic compositions comprising microencapsulated antigens. Amsden, which describes processes for production of microspheres with dispersed bioactive agents, discloses N-carboxymethyl chitosan as one of the many reagents suitable for preparation of microspheres. The Examiner concludes that the combined disclosure of Eyles and Amsden would have made the claims obvious to one of ordinary skill in the art in

the area of the present application, at its priority date, because one of ordinary skill in the art would have had found it found it obvious to use N-carboxymethyl chitosan to modify the compositions described in Eyles in order to enhance their mucoadhesive properties and mucosal adsorption. The Examiner states on pages 7-8 of the Office Action that one of ordinary skill in the art would have had a reasonable expectation of success that such a modification would achieve enhanced mucosal adsorption because N-carboxymethyl chitosan microspheres described in Amsden are composed of biodegradable, biocompatible polymer.

Applicants respectfully remind the Examiner that MPEP 2141 and 2143 require a clear articulation of reasons why the claims would have been obvious in order to support the rejection under 35 U.S.C. §103. The Office Action fails to clearly articulate such reasons. At a minimum, the Office Action does not explain why one of ordinary skill in the art would have expected that the modification of the antigen-containing microspheres prepared of a biodegradable, biocompatible polymer, poly-(L-lactide) (as disclosed in Eyles), with another biodegradable, biocompatible polymer, N-carboxymethyl chitosan (as disclosed in Amsden), would result in any further improvement the mucoadhesive or other properties of the microspheres. Applicants therefore submit that the articulated reasoning as to why the claims would have been obvious is absent from the Office Action, and it therefore fails to establish a *prima facie* case of obviousness for at least this reason.

*The Claimed Compositions Possess an Unexpected Advantage when Compared to the Combined Disclosure of Eyles and Amsden*

Both Eyles and Amsden discuss microencapsulation of biologically active compounds. Some advantages of applying microencapsulation to antigenic compounds were known at the priority date of the present application, as discussed in its specification, for example, on page 2, lines 15-30. Eyles is a research article dedicated to comparative testing of several specific compositions containing a specific microencapsulated antigen. Thus limited in scope, Eyles describes only one version of such microencapsulated compositions, poly-(L-lactide) microspheres, and does not disclose or suggest co-microencapsulating an antigen and an adjuvant. Amsden, on the other hand, is devoted generally to processes of microencapsulation of bioactive compounds, and, naturally, describes a number of possible polymers suitable for

preparation of microspheres. However, Amsden does not articulate any particular advantage of using N-carboxymethyl chitosan, which is listed as one of many potential polymers for the production of microspheres.

The claims are directed to compositions comprising at least three components (not two, as the Examiner states on page 10, first full paragraph, of the Office Action), which are a biologically active agent capable of generating a protective immune response in an animal or a human, N-carboxymethyl chitosan or a salt thereof in an amount of 0.1 to 10% w/w, and a polymeric material of a molecular weight of 94 kDa or more. The biologically active agent and N-carboxymethyl chitosan are both microencapsulated in microspheres or microparticles comprising the polymeric material. One unexpected advantage achieved by applicants by combining all three components in the pharmaceutical compositions recited in the claims is that N-carboxymethyl chitosan acts as an adjuvant, improving an immunogenic effect of the microencapsulated antigen. This unexpected advantage is described in the specification of the present application, for example, on page 3, lines 22-28, page 4, line 23, page 20, line 29, through page 21, line 20, and in Figure 4. The Office Action fails to address this unexpected advantage.

*The Examiner Uses Impermissible Hindsight when Proposing the Claimed Compositions Based on the Combination of Eyles and Amsden*

It is important for obviousness analysis to identify a reason that would have prompted one of ordinary skill in the art to combine the known elements in the same way as they are combined in the claims. *KSR Int'l Co. v Teleflex Inc.*, 550 U.S. 398, 401 (2007). However, it is not clear either from the combination of Eyles and Amsden, or from the Examiner's analysis provided in the Office Action why one of ordinary skill in the art would combine poly-(L-lactide), an antigen, and N-carboxymethyl chitosan in the same microsphere, as proposed by the Examiner, in order to arrive at the claimed compositions. Applicants submit that the Examiner proposes adding N-carboxymethyl chitosan to poly-(L-lactide) antigen-containing microspheres based on the insight into adjuvant properties N-carboxymethyl chitosan used as a component of microspheres, which is based on the description provided in the present application. Accordingly, the Examiner's conclusion of obviousness is based on improper hindsight

reasoning, as discussed in MPEP 2145(X)(A) and cases cited therein. Applicants therefore assert that the rejection is improper for at least this reason.

*The Combination of Eyles and Amsden Fails to Disclose or Suggest the Combination of Elements Recited in the Rejected Claims*

Applicants reiterate that a combination of Eyles and Amsden does not disclose or suggest a combination of the elements of the rejected claims. Amsden teaches that antigens can be microencapsulated into the microspheres made of a variety of polymers, including N-carboxymethyl chitosan. Applicants were unable to identify any passage in Amsden supporting the Examiner's assertion on page 9, first full paragraph, of the Office Action, that Amsden teaches vaccines that affects or utilize mucosal surfaces as portals of entry. Applicants respectfully request the Examiner to identify the relevant material in Amsden to support this statement. As the Examiner discusses on page 9 of the Office Action, Eyes teaches that microencapsulation of antigens may protect vaccines from degradation and enhance adsorption. However, combined teachings of Amsden and Eyles fail to disclose or suggest a microencapsulated composition that contains an antigen, an immunostimulating amount of N-carboxymethyl chitosan and a separate microencapsulating polymer.

Applicants wish to draw the Examiner's attention to the rejected claims, which, contrary to the statements on page 10 of the Office Action (see paragraph 6), in fact, recite an immunostimulating amount of N-carboxymethyl chitosan or a salt thereof, 0.1 to 10% w/w, encapsulated in microspheres or microparticles. Applicants submit that the combination of Eyles and Amsden fails to teach or suggest microspheres comprising the immunostimulating amount of N-carboxymethyl chitosan or a salt thereof, encapsulated in microspheres or microparticles, as recited in the claims. Contrary to the statement by the Examiner on page 9 of the Office Action, the claims recite a structural feature not found in the cited combination of documents, and not merely intended use of the composition.

*The Range of Immunostimulating Amounts of N-carboxymethyl chitosan Recited in the Claims is Nonobvious in View of the Combination of Eyles and Amsden*

On page 10, last paragraph of the Office Action, the Examiner asserts that Amsden teaches polycationic carbohydrates capable of forming particles from 99:1 to 9:1 w/w. Applicants were unable to locate the relevant teaching in Amsden and respectfully request the Examiner to provide the citation to the specific passage or passages in Amsden supporting the above statement. The Examiner cites to *Ex Parte Rassmussen* (POB 1959) 123 USPQ 498, stating that no more than routine skill is involved in adjusting the amount of a component of a well known composition to suit a particular starting material in order to achieve the results taught in the prior art. Applicants respectfully bring to the Examiner's attention that this rule is not applicable to the present rejection because the result achieved by the rejected claims, an unexpected improvement of immunogenic properties of microencapsulated antigen by co-encapsulation of a particular range of amounts of N-carboxymethyl chitosan, is not taught or suggested in the combination of Eyles and Amsden.

As discussed in MPEP 2144.05(II)(B) and the cases cited therein, a particular parameter must first be recognized as a variable which achieves a recognized result, before the determination of the optimum of variable's workable ranges might be characterized as routine experimentation. Eyles is completely silent on the use of N-carboxymethyl chitosan in microspheres, while Amsden fails to explicitly define the final quantity of N-carboxymethyl chitosan in the prepared microspheres and is silent on its potential immunostimulating properties. In the absence of a recognition of N-carboxymethyl chitosan's adjuvant properties, the determination of the range of immunostimulating amounts of N-carboxymethyl chitosan to be co-encapsulated into polymeric microspheres or microparticles along with a biologically active agent capable of generating a protective immune response in an animal or a human, as recited in the claims, is not routine experimentation and is nonobvious in view of the combination of Eyles and Amsden.

Applicants assert that that the rejected claims would not have been obvious to one of ordinary skill in the art based on the combined disclosure of Eyles and Amsden at least due to the reasons discussed above. In view of the claim amendments and the foregoing remarks,

applicants request withdrawal of the rejection of the claims as obvious over Eyles in view of Amsden.

***Illum (WO 97/20576; “Illum”) and Amsden et al. (WO 99/57176; “Amsden”)***

The Examiner rejects Claims 52, 56, 58, 59, 61, 66, 68-69 and 72-73 under 35 U.S.C. §103(a) as obvious over Illum in view of Amsden. Applicants cancel Claims 52, thereby rendering its rejection moot. Applicants request the Examiner to withdraw the rejection of Claims 56, 58, 59, 61, 66, 68-69 and 72-73 at least due to the reasons discussed below.

**Dependent Claims 66 and 68-69 are Nonobvious in View of Eyles and Amsden at Least for the Same Reasons Claim 63 is Nonobvious**

The Examiner does not reject Claim 63 in this section. Applicants therefore conclude that the Examiner finds that the combination of elements recited in Claim 63 would have been nonobvious to one of ordinary skill in the art in the area of the present application, at its priority date. Applicants amend Claim 66 to depend on Claim 63. Applicants submit to the Examiner’s attention that Claims 66 (as currently amended) and Claims 68-69 (as previously presented) are dependent, directly or indirectly, on Claim 63. Accordingly, Claims 66 and 68-69 recite at least the same combination of elements as Claim 63 and should be found nonobvious in view of Illum and Amsden for at least the same reasons Claim 63 is nonobvious. Applicants request the Examiner to issue appropriate statements and withdraw the rejection of Claims 66 and 68-69.

**Nonobviousness of Claim 72 and Its Dependent Claims 56, 58, 59, 61 and 73**

Applicants assert that the combination of Illum and Amsden fails to render obvious Claim 72 and its dependent Claims 56, 58, 59, 61 and 73. Applicants discussed the scope and content of Illum and Amsden in the previous responses. Applicants maintain the positions stated in the previous responses and respectfully request the Examiner to refer to their previously submitted remarks characterizing the cited documents. The scope and content of Amsden is further addressed in the previous sections of this Response, as are the pending claims.

Illum discloses vaccine compositions comprising antigen and a chitosan. The only chitosans disclosed in Illum as adjuvants for mucosal vaccination are chitosan salts, such as

chitosan glutamate. Illum is completely silent on compositions comprising N-carboxymethyl chitosan, which is an element of the pending claims. As discussed in the previous section of this Response, Amsden teaches that N-carboxymethyl chitosan is one of many compounds suitable for forming polymeric microparticles. The Examiner concludes that the combined disclosure of Illum and Amsden would have made the claims obvious to one of ordinary skill in the art in the area of the present application, at its priority date, because one of ordinary skill in the art would have had found it obvious to use N-carboxymethyl chitosan to modify the compositions described in Illum to enhance their mucoadhesive properties, mucosal adsorption and immunostimulant activity.

Applicants submit that the Examiner fails to articulate why one of ordinary skill in the art would have been motivated to use N-carboxymethyl chitosan when any discussion of any of its advantageous properties, mucoadhesive or immunogenic, is absent from the combined disclosure of Illum and Amsden. Applicants therefore submit that the articulated reasoning as to why the claims would have been obvious is absent from the Office Action, and it therefore fails to establish a *prima facie* case of obviousness for at least this reason. Furthermore, Applicants submit that the Examiner proposes using N-carboxymethyl chitosan in the compositions disclosed in Illum based on the insight into adjuvant properties N-carboxymethyl chitosan, when used as a component of microspheres, which is gained from the description provided in the present application. Accordingly, the Examiner's conclusion of obviousness is based on improper hindsight reasoning, as discussed in MPEP 2145(X)(A) and cases cited therein. Applicants therefore assert that the rejection is improper for at least this reason.

Applicants further submit that the combination proposed by the Examiner would not result in the rejected claims. If one of ordinary skill in the art in the area of the present application were to combine the teachings of Illum and Amsden, she still would not arrive at Claim 72 or any of its dependent claims. As stated by the Examiner on page 14 of the Office Action it would have been "*prima facie* obvious at the time of applicants invention to have used the known N-carboxymethyl chitosan as taught by Amsden and modify the compositions to include the biologically active agents capable of generating a protective immune response and providing the compositions in a microparticle formulation as taught by Illum to enhance the mucoadhesive properties" means encapsulating a biologically active agent in polymeric



microspheres of N-carboxymethyl chitosan. This modification would result in the microspheres that are structurally different from the compositions recited in Claim 72 and its dependent claims.

Furthermore, as discussed above, Amsden fails to teach or suggest the range of N-carboxymethyl chitosan concentrations recited in the claims. Since neither Amsden, nor Illum suggest that N-carboxymethyl chitosan possessed immunostimulating properties, it would have been nonobvious to use the general teaching of Amsden regarding N-carboxymethyl chitosan to arrive at the specific range of immunostimulating amounts recited in the claims. Applicants assert that, prior to the applicants' invention of the claimed pharmaceutical compositions, it would not have been obvious to one of ordinary skill in the art to select N-carboxymethyl chitosan from the list of polymers suitable for microsphere production taught in Amsden, determine its immunostimulating amount, and use of such an amount with the vaccine compositions disclosed in Illum, in order to arrive at the pending claims.

Applicants assert that that the rejected claims would not have been obvious to one of ordinary skill in the art based on the combined disclosure of Illum and Amsden at least due to the reasons discussed above. In view of the claim amendments and the foregoing remarks, applicants request withdrawal of the rejection of the claims as obvious over Illum and Amsden.

*Amsden and Eyles in view of Cleary et al. (WO 96/21432; "Cleary")*

The Examiner rejects Claim 63 under 35 U.S.C. §103(a) as obvious over Amsden and Eyles and further in view of Cleary. Applicants respectfully assert that the combination of the publications cited by the Examiner fails to render Claim 63, as currently amended, obvious. Applicants respectfully disagree with the Examiner's obviousness analysis provided in the Office Action.

The scope and content of Amsden, Eyles and Cleary was discussed in the previous responses. Applicants maintain the positions stated in the previous responses and respectfully request the Examiner to refer to their previously submitted remarks characterizing the cited documents. Amsden and Eyles are also discussed in the prior sections of the current Response. Eyles describes microencapsulation as a way to preserve the integrity of bioactive agents,

Amsden teaches that N-carboxymethyl chitosan is suitable for forming polymeric microparticles, and Cleary discloses particles comprising an active substance and a mucoadhesive bioerodible polymer. According to Cleary, the mucoadhesive particles can be produced by uniformly mixing an active substance with a mucoadhesive polymer or by coating the active substance core with a layer of the mucoadhesive polymer

Applicants assert that the combined teaching of the three documents do not disclose all elements of a pharmaceutical composition recited in Claim 63, which reads, as currently amended:

“A pharmaceutical composition comprising a polymeric microparticle surface-modified or coated with N-carboxymethyl chitosan or a salt thereof, which has adsorbed thereon a biologically active agent capable of generating a protective immune response in an animal or a human.”

The Examiner appears to acknowledge the structural differences between the composition recited in Claim 63 and the compositions she proposed based on the combined disclosure of Amsden, Eyles and Cleary in the sentence bridging pages 15 and 16 of the Office Action: “Cleary et al teach a particle having a drug containing core and a mucoadhesive coating made of a polymer that dissolves slowing.....” Cleary indeed teaches, for example, on page 7, lines 5-8, slowing the release of active agents by coating them with a mucoadhesive polymer, in order to prolong the retention of the active agent on the mucosal surface for an extended time.

Applicants assert that it would not have been obvious to one of ordinary skill in the art using the combined disclosure of Amsden, Eyles and Cleary to arrive at polymer microspheres surface-modified with N-carboxymethyl chitosan and having adsorbed thereon a biologically active agent, as recited in Claim 63. All of the cited publications fail to suggest that adding N-carboxymethyl chitosan to the immunogenic polymer microparticles would result in any further improvement of the particles’ immunogenic, mucoadhesive or other properties, and fail to suggest that adsorbing the antigen onto the particles surface-modified or coated with N-carboxymethyl chitosan would result in any improvement in the particles’ properties.

The Examiner asserts on page 16 of the Office Action that one of ordinary skill in the art in the area of the present application would have been motivated to modify the particles

discussed in Cleary with N-carboxymethyl chitosan, as recited in Claim 63, in order to arrive at the claimed composition, because both Amsden and Eyles teach the inclusion of a mucoadhesive. Applicants respectfully bring to the Examiner's attention that such a modification would not result in the claimed pharmaceutical composition, at least because, as discussed above, Cleary does not describe or suggest the particles in which an antigen is adsorbed onto the surface of the particles. Cleary suggests that a biologically active agent should be at least uniformly mixed with or coated with the polymer, in order to control the dissolution of the particle and improve retention of the biologically active agent on the mucosal surface.

Adsorbing the antigen onto the surface of the particles, as recited in Claim 63, would be contrary to the goals Cleary attempted to achieve, namely, the slowing of the dissolution of a biologically active agent. Applicants respectfully remind the Examiner that when the proposed modification changes the principle of operation of what is disclosed in the references, then the references are not sufficient to render the claims *prima facie* obvious. *See* MPEP 2143.02(VI), citing *In re Ratti*, 270 F.2d 810 (CCPA 1959). Applicants assert that the modification proposed by the Examiner changes the principle of operation of the particles disclosed in Cleary, and the Office Action fails to establish *prima facie* obviousness for at least this reason.

The Examiner then states that all of the claimed elements were known in the prior art and one of ordinary skill in the art could have combined the elements, as claimed, by known methods with no change in their respective functions, and the combinations would have yielded predictable results (emphasis added). However, Amsden and Eyles, as well as Cleary, fail to disclose or suggest using N-carboxymethyl chitosan as a mucoadhesive polymer. Amsden is the only cited document discussing N-carboxymethyl chitosan, as one of the many polymers suitable for microparticle formation. On the other hand, as applicants discussed in the prior sections of this Response, the combination of the elements in the claimed compositions yielded unexpectedly advantageous result, enhancement of immunogenic properties of an antigen. Applicant respectfully remind the Examiner that, as discussed in MPEP 2143.01(III), the fact that references can be combine or modified does not render the claim obvious unless the results would have been predictable to one of ordinary skill in the art. Applicants assert that the Office Action fails to establish obviousness of Claim 63 for at least this reason.

Applicants assert that a combination of Eyles, Amsden and Clearly fails to render obvious Claim 63 for at least the reasons set forth above and request withdrawal of the rejection.

**Objections to Claims 63 and 66**

The Examiner objects to Claims 63 and 66 due to informalities. Applicants submit that the claim amendments in this Response correct the informalities and request that the objections be withdrawn.

## **CONCLUSION**

This Response fully addresses the rejections in the Office Action. Based upon the amendments and remarks provided above, applicants believe that the pending claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 11-0855.

If the Examiner believes any informalities remain in the application that may be corrected by an Examiner's Amendment, or that there are any other issues that can be resolved by a telephone interview, a telephone call to the undersigned attorney at (404) 815-6102 is respectfully solicited.

Respectfully submitted,

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